A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP12215.

Ambient Air Pollution and Risk of Enterotomy, Gastrointestinal Cancer, and All-Cause Mortality among 4,708 Individuals with Inflammatory Bowel Disease: A Prospective Cohort Study

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Background: Previous studies indicated that air pollution plausibly increases the risk of adverse outcomes in inflammatory bowel disease (IBD) via proinflammatory mechanisms. However, there is scant epidemiological data and insufficient prospective evidence assessing associations between ambient air pollution and clinical outcomes of IBD.

Objectives: We aimed to investigate the associations between ambient air pollution and clinical outcomes among individuals with IBD.

Methods: Leveraging data from the UK Biobank, we included 4,708 individuals with IBD recruited in the period 2006–2010 in this study. A land use regression model was used to assess annual mean concentrations of ambient air pollutants nitrogen including oxides (NO_x), nitrogen dioxide (NO_2), and particulate matter (PM) with aerodynamic diameter $\leq$10 μm (PM_{10}) and PM with aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$). Individuals with IBD were followed up for incident clinical outcomes of enterotomy, gastrointestinal cancer, and all-cause mortality, ascertained via death registry, inpatient, primary care, and cancer registry data. Cox proportional hazard model was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the magnitude of the associations.

Results: During a mean follow-up of 12.0 y, 265 enterotomy events, 124 incident gastrointestinal cancer, and 420 death events were documented among individuals with IBD. We found that each interquartile range (IQR) increase in exposure to $PM_{2.5}$ was associated with increased risk of enterotomy (HR = 1.16; 95% CI: 1.00, 1.34, $p = 0.043$), whereas an IQR increase in exposure to NO_x (HR = 1.10; 95% CI: 1.01, 1.20, $p = 0.016$), NO_2 (HR = 1.16; 95% CI: 1.03, 1.29, $p = 0.010$), PM_{10} (HR = 1.15; 95% CI: 1.03, 1.30, $p = 0.015$), and $PM_{2.5}$ (HR = 1.14; 95% CI: 1.02, 1.28, $p = 0.019$) was associated with increased risk of all-cause mortality among individuals with IBD. We did not observe any significant associations between air pollutants and gastrointestinal cancer in the primary analyses. Consistent results were observed in subgroup and sensitivity analyses.

Conclusions: Ambient pollution exposure was associated with an increased risk of enterotomy and all-cause mortality among individuals with IBD, highlighting the important role of environmental health in improving the prognosis of IBD. https://doi.org/10.1289/EHP12215

Introduction

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic immune-mediated digestive disease that poses a substantial burden worldwide.[1] As an important environmental exposure for the global population,[2] air pollution has been linked to both the onset and prognosis of IBD via an increase in inflammatory cytokines and damage to the colonic mucosa in laboratory research.[3,4] However, scant epidemiological studies have examined the associations of air pollution with adverse outcomes among individuals with IBD.[5,6] One ecological study using data from 72 counties in Wisconsin showed that a 1-log increase in the density of total criteria pollutant emission was associated with a 40% increase in the rate of IBD hospitalizations.[5]

According to current expert consensus under the auspices of the International Organization for the Study of Inflammatory Bowel Diseases, enterotomy, gastrointestinal cancer, and all-cause mortality risk are important clinical outcomes to be managed in terms of medium to long-term prognosis of IBD.[7] In the general population, multiple studies have demonstrated an association of air pollution with perforation, gastrointestinal cancers, and mortality.[8,9] However, whether air pollution is associated with the adverse outcomes of IBD remains unknown.

Here, we performed a prospective cohort study to evaluate the associations of four common air pollutants, nitrogen oxides (NO_x), nitrogen dioxide (NO_2), and particulate matter (PM) with aerodynamic diameter $\leq$10 μm (PM_{10}) and PM with aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$), with the risk of enterotomy, gastrointestinal cancer, and all-cause mortality among individuals with IBD. Based on the previous literature that air pollutants lead to adverse outcomes by triggering inflammation,[10] we also explored the mediation effect of conventional serum inflammation biomarkers using a mediation analysis.

Material and Methods

Study Population

UK Biobank is an ongoing national prospective cohort study that enrolled more than 500,000 volunteers in 22 recruitment centers across the United Kingdom between 2006 and 2010.[11] At recruitment centers, participants signed an electronic consent and received a touch-screen questionnaire, a computer-assisted interview, physical measurements, and sample collection. The North

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Supplemental Material is available online (https://doi.org/10.1289/EHP12215).
All authors declare that they have nothing to disclose.
Received 30 September 2022; Revised 9 July 2023; Accepted 11 July 2023; Published 28 July 2023.

West–Haydock Research Ethics Committee granted ethical approval to use the UK Biobank database (REC reference: 21/NW/0157). This study was conducted with the UK Biobank Resource under application number 73595 and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

The identification of individuals with IBD has been described before.[12] Specifically, individuals with IBD were identified via self-report, primary care, and hospital inpatient data recorded in the *International Classification of Diseases 10th revision* (ICD-10), *ICD ninth revision* (ICD-9), or other specific diagnosis codes that can be converted into ICD-10 with specific mappings. Baseline IBD was defined as being diagnosed before recruitment using ICD-10 codes K50 and K51 and ICD-9 codes 555 and 556. We also identified phenotypes by disease location and behavior using ICD-10 coding data sets that were validated in Swedish National Patient Register[13] and developed in the UK Biobank (Table S1).[12] We included 5,747 individuals with IBD and excluded participants with missing air pollutants data ($n = 537$), participants who died within the first year of follow-up ($n = 16$), participants who had any cancer at baseline or had gastrointestinal cancer within the first-year follow-up ($n = 418$), or participants who moved to another address at repeat assessments ($n = 68$). Finally, 4,708 individuals with IBD were included in the primary analysis (Figure S1).

Assessment of Air Pollution

Four air pollutants, NO_x, NO_2, PM_{10}, and $PM_{2.5}$, were selected according to the air pollution criteria by the World Health Organization[14] and European Commission[15] based on the data availability of the UK Biobank. As part of European Study of Cohorts for Air Pollution Effects, air pollution variables in UK Biobank were estimated by land use regression models using the predictor variables obtained from the Geographic Information System.[16,17] The (x, y) coordinates of the UK Biobank participants were overlaid on these maps (projected to the British National Grid), and the corresponding air pollution concentrations for the 100 m × 100 m grid cells were assigned to the coordinates. The land use regression models showed good model performance in London, with cross-validation R^2 of 77%, 88%, 87%, and 88% for $PM_{2.5}$, PM_{10}, NO_2, and NO_x, respectively.[16,17] Previous studies also indicated that most air pollution temporal trend fluctuations were generally stable over the study period in the UK Biobank and that average values of air pollution can be used as a proxy measure for long-term exposure.[18–21] Air pollution estimates for $PM_{2.5}$ and NO_x were only available for the year 2010, whereas NO_2 (2005–2007 and 2010) and PM_{10} (2007 and 2010) had the exposure data for several years; thus we used the mean values of NO_2 and PM_{10} over years in the analysis.

Ascertainment of Outcomes

Outcomes of interest were obtained from the longitudinal medical records of participants via linkage to external national data, including inpatient data (Hospital Episode Statistics for England, Scottish Morbidity Record, and Patient Episode Database for Wales), cancer registry data, and death data.

The clinical outcomes of interest were enterotomy, incident gastrointestinal cancer, and all-cause mortality. The enterotomy was defined as small bowel resection and colectomy by the Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS-4) via inpatient data. Detailed coding of enterotomy was based on the Surgical Workload and Outcomes Research Database, which is a quality improvement program run jointly by the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the Association of Laparoscopic Surgeons of Great Britain and Ireland, and Methods Analytics Ltd.[22] The inpatient data also provide a source of data regarding admission to hospital that can distinguish between elective surgery and emergency surgery. Gastrointestinal cancer was defined as gastric cancer, small intestinal cancer, and colorectal cancer by ICD-10 and ICD-9 codes via inpatient data, primary care data, and cancer registry. The death events were obtained via the death registry. Two specific causes of death, i.e., cancer- and cardiovascular-specific mortality, were considered as secondary outcomes, because both of them are the leading causes of death and are associated with air pollution.[8,9,23] Specific causes of death were defined using the following ICD-10 codes: cancer (C00-D48) and cardiovascular disease (I00-I79).[23]

The detailed diagnostic codes for enterotomy and gastrointestinal cancer are presented in Table S2. Moreover, The Audit Commission review of 2009 to 2010 concluded procedural coding OPCS-4 overall accuracy of 90% and diagnostic coding ICD-10 overall accuracy of 89%.[24] For each outcome, follow-up time was calculated from the time the participants were first recruited in the UK Biobank to the time of the first recording of the corresponding outcomes (enterotomy, gastrointestinal cancer, all-cause mortality), death, date of loss to follow-up, or end of follow-up, whichever occurred first.

Assessment of Covariate

The following variables were considered potential confounders based on previous studies.[3,25,26] Information assessed by self-reported questionnaires included age, education level (college, below college), smoking status (never smoked, previous or current smoker), family history of bowel cancer (with, without), assessment centers (England, Wales, and Scotland), whether using open gas or solid fuel fire for cooking/heating (yes, no), smokers in the household (none, at least one), and exposure to tobacco smoke at home (yes, no). Household income was categorized into "less than" or "equal to or above" £31,000 categories, being closest to the UK median gross household income (£27,789) in 2009–2010. Ethnicity was categorized into "White" (White, British, Irish, and any other White background) and "Others" (Mixed, Asian or Asian British, Black or Black British, Chinese, and other ethnic groups), based on the self-reported items. Ethnicity other than White was categorized as "Others" because their number was limited in the study sample (Table 1). Townsend deprivation index (TDI) was included as the measure of material deprivation within the population,[27] derived by postcodes of participants in the UK Biobank (range for current sample, −6.3 to 10.6, with higher value representing a higher deprivation). Dietary factors were obtained from the food frequency questionnaire, which showed good agreement between reported consumption at recruitment and the repeat assessment center visit, ∼4 y later.[28] Based on the recommendation by the American Heart Association to define food intake beneficial to cardiometabolic health,[29,30] we calculated a healthy diet score according to the frequency of seven food groups (fruits, vegetables, processed meats, unprocessed red meat, fish, whole grains, refined grains). The diet score was constructed by the previous study in UK Biobank[31] and found to be inversely associated with incident IBD.[32] As recommended by these studies, we defined healthy or unhealthy diets based on whether a healthy diet score ≥4. Body mass index (BMI) was calculated using height and weight measured in the physical examination. Physical activity was collected using a validated short International Physical Activity Questionnaire and assessed as adequate or inadequate based on the recommendation from the American Heart Association.[29] Adequate physical activity was defined as 150 min moderate activity per week, or ≥75 min vigorous activity per week, or equivalent combination, or moderate physical activity at least 5 d a week or vigorous activity once a week. Alcohol consumption was estimated via 19-item touch-screen

questionnaires that were described before.[31] None to moderate level of alcohol consumption was defined as 0–14 g/d for women and 0–28 g/d for men, according to U.S. dietary guidelines,[33] above which is defined as heavy level. Baseline systolic blood pressure and diastolic blood pressure were measured by Omron digital blood pressure monitor. Baseline lipid traits [cholesterol, triglycerides, and apolipoprotein a were measured by enzymatic or immune-turbidimetric methods on the platform (AU5800; Beckman Coulter)]. Baseline comorbidities were measured by Charlson Comorbidity Index. Charlson Comorbidity Index was constructed based on 17 comorbidities with assigned weights associated with ICD codes from inpatient data.[34] The medication information was obtained from baseline touch-screen questionnaires and verbal interviews, including use of nonsteroidal anti-inflammatory drugs, aminosalicylates, corticosteroids, and immunomodulators. If covariate information was missing or recorded as "unknown," we imputed the median values for continuous variables or applied a most frequently used category for categorical variables. We provide more details of the covariate process in Table S3.

We selected 14 potential indicators measured at baseline involving inflammatory processes based on prior literature,[26,35] including counts of basophil, eosinophil, lymphocyte, leukocyte, monocyte, and platelet, erythrocyte distribution width, lymphocyte percentage, monocyte percentage, neutrophil to leukocyte count ratio, neutrophil to lymphocyte count ratio, platelet to lymphocyte count ratio, C-reactive protein, and INFLA-score. The INFLA-score contained C-reactive protein, white blood cell, platelet count, and the neutrophil to lymphocyte ratio, synergistically having a proinflammatory role in different biological processes of the immune response.[36] To compute the INFLA-score, all four components, laying in the highest deciles (seventh to 10th) were assigned values from +1 to +4; whereas biomarker levels laying in the lowest deciles (first to fourth) were given values from −4 to −1.

Statistical Analysis

Baseline characteristics of individuals with IBD, CD, and UC were summarized as means with standard deviations (SD) for continuous variables and percentages for categorical variables. Correlation between air pollutants was reported using Pearson correlation coefficients. The Cox model was applied to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between ambient air pollution [per interquartile range (IQR) increment and in quartiles] and risk of enterotomy, gastrointestinal cancer, and all-cause mortality. We also explored the associations between ambient air pollution and risk of enterotomy by admission source (elective or emergency admission) and cause-specific mortality. Two multivariable models were constructed: The minimally adjusted model was adjusted for age, sex, and ethnicity; the fully adjusted model was further adjusted for assessment centers, household income, smoking status, BMI, physical activity, education level, alcohol consumption, healthy diet, and medication (use of nonsteroidal anti-inflammatory drugs, aminosalicylates, corticosteroids, and immunomodulators). We additionally adjusted baseline enterotomy history when treating enterotomy as outcomes based on the fully adjusted model. Systolic blood pressure, diastolic blood pressure, cholesterol, triglycerides, apolipoprotein (a), and family history of bowel cancer (only for gastrointestinal cancer) were included in the fully adjusted model when treating gastrointestinal cancer and mortality as outcomes. The proportional hazards assumptions of all Cox models were confirmed by the weighted residual method,[37] and the smallest p-value was 0.34.

For significant associations observed in the primary analysis, we conducted mediation analysis as a secondary analysis to explore whether inflammation status mediated the associations between air pollutants and adverse outcomes of IBD. Mediation analysis distinguishes the direct effect of specific air pollution exposure on the risk of adverse outcomes, and the indirect effect mediated by inflammation status. Multivariable linear regression between each potential biomarker and air pollutants based on the fully adjusted model was first applied. Those showing significant associations with air pollution were chosen as mediators to present inflammation status in the following mediation analysis. The proportion of associations mediated by selected inflammation-related mediators was calculated as [indirect effect/(indirect + direct effect)].

Subgroup analyses stratified by age, sex, healthy diet, smoking status, and physical activity were conducted to explore potential interactive factors based on prior knowledge in investigating associations of air pollution with mortality and other health-related outcomes.[38,39] The p-interaction was calculated by testing the change of goodness-of-fit before and after allowing a multiplication term of the air pollution (per IQR) and these covariates. For sensitivity analysis, based on the fully adjusted model, we further: *a*) restricted to individuals who had lived at the current address more than 10 y before baseline ($n = 3,283$); *b*) adjusted for Charlson comorbidity index; *c*) adjusted for baseline duration of IBD; *d*) adjusted for indoor air pollution-related variables (gas or solid fuel for cooking/heating, smokers in the household, exposure to tobacco smoke at home); *e*) adjusted for TDI instead of household income; *f*) excluded gastrointestinal cancer ($n = 30$) or death events ($n = 40$) in the first 3 y of follow-up; *g*) excluded individuals with a baseline history of enterotomy ($n = 402$); and *h*) performed a competing risk model to account for the competing risk of death when investigating the associations between air pollution and gastrointestinal cancer using the R package "cmprsk."

All statistical analyses were performed using R (version 4.2.1; R Development Core Team). Mediation analysis was conducted using the R package "BruceR" with 1,000 bootstrap samples to estimate bias-corrected bootstrap CI. All statistical tests were two-sided, and a p-value <0.05 was statistically significant.

Results

Baseline Characteristics

The baseline characteristics of individuals with IBD, CD, and UC are shown in Table 1. Of the 4,708 individuals with IBD, 2,443 (51.9%) were female and 3,223 (68.4%) were with UC. The mean ± SD age was 57.0 (7.9) y in individuals with IBD, 56.1 (8.1) y in individuals with CD, and 57.3 (7.9) y in individuals with UC. We documented 265 enterotomy events (184 elective and 81 emergency surgery), 124 incident gastrointestinal cancer, and 420 death events (144 cardiovascular disease-specific and 204 cancer-specific death events) during a mean follow-up of 12.0 y. Annual mean ± SD exposure of NO_x, NO_2, PM_{10}, and $PM_{2.5}$ among individuals with IBD were 43.9 (15.0), 29.0 (8.9), 19.3 (1.9), 10.0 (1.1) $\mu g/m^3$, respectively. As shown in Table 2, strong correlations were observed between air pollutants with Pearson correlation coefficients ranging from 0.652 to 0.864.

Primary Analysis

As shown in Table 3, the risk of enterotomy would be 16% higher (HR = 1.16; 95% CI: 1.00, 1.34, $p = 0.043$) among individuals with IBD and 24% higher (HR = 1.24; 95% CI: 1.04, 1.47, $p = 0.017$) in CD per IQR increment in $PM_{2.5}$ (1.3 $\mu g/m^3$). The associations between $PM_{2.5}$ and the risk of enterotomy in UC were not

Table 1. Baseline characteristics of study sample in the UK Biobank recruited during the period 2006–2010 among participants with IBD.

	Overall ($n = 470$)	CD ($n = 1,485$)	UC ($n = 3,223$)
Age at baseline [y (mean ± SD)]	57.0 (7.9)	56.1 (8.1)	57.3 (7.9)
Sex [*n* (%)]			
Female	2,443 (51.9)	838 (56.4)	1,605 (49.8)
Male	2,265 (48.1)	647 (43.6)	1,618 (50.2)
Townsend deprivation index (mean ± SD)	−1.3 (3.0)	−1.1 (3.1)	−1.4 (2.9)
Household income [*n* (%)]			
<£31,000	2,776 (59.0)	907 (61.1)	1,869 (58.0)
≥£31,000	1,885 (40.0)	559 (37.6)	1,326 (41.1)
Missing	47 (1.0)	19 (1.3)	28 (0.9)
Education [*n* (%)]			
Below college degree	3,343 (71.0)	1,079 (72.7)	2,264 (70.2)
College degree	1,284 (27.3)	377 (25.4)	907 (28.1)
Missing	81 (1.7)	29 (2.0)	52 (1.6)
Ethnicity[a] [*n* (%)]			
White	4,489 (95.3)	1,432 (96.4)	3,057 (94.8)
Others	197 (4.2)	47 (3.2)	150 (4.7)
Missing	22 (0.5)	6 (0.4)	16 (0.5)
BMI (mean ± SD), kg/m^2	27.2 (4.6)	26.9 (4.7)	27.3 (4.6)
Physical activity [*n* (%)]			
Inadequate	1,592 (33.8)	551 (37.1)	1,041 (32.3)
Adequate	3,116 (66.2)	934 (62.9)	2,182 (67.7)
Smoking status [*n* (%)]			
Never smoked	2,227 (47.3)	667 (44.9)	1,560 (48.4)
Previous or current smokers	2,462 (52.3)	813 (54.7)	1,649 (51.2)
Missing	19 (0.4)	5 (0.3)	14 (0.4)
Smokers in household [*n* (%)]			
None	4,256 (90.4)	1,349 (90.8)	2,907 (90.2)
At least one	452 (9.6)	136 (9.2)	316 (9.8)
Missing	—	—	—
Alcohol consumption [*n* (%)]			
None to moderate	803 (17.1)	215 (14.5)	588 (18.2)
Heavy	3,892 (82.7)	1,265 (85.2)	2,627 (81.5)
Missing	13 (0.3)	5 (0.3)	8 (0.2)
Healthy diet [*n* (%)]			
Unhealthy	1,544 (32.8)	549 (37.0)	995 (30.9)
Healthy	2,933 (62.3)	863 (58.1)	2,070 (64.2)
Missing	231 (4.9)	73 (4.9)	158 (4.9)
Open Gas or solid fuel fire for cooking/heating [*n* (%)]			
Yes	530 (11.3)	175 (11.8)	355 (11.0)
No	4,133 (87.8)	1,292 (87.0)	2,841 (88.1)
Missing	45 (1.0)	18 (1.2)	27 (0.8)
Baseline history of enterotomy [*n* (%)]	402 (8.5)	218 (14.7)	184 (5.7)
Baseline duration of IBD (mean ± SD), y	17.1 (12.6)	17.9 (12.8)	16.9 (12.6)
Charlson comorbidity index (mean ± SD)	0.3 (0.7)	0.3 (0.8)	0.3 (0.7)
Disease extent [*n* (%)]			
Ileal CD	158 (3.4)	158 (10.6)	NA
Colonic CD	198 (4.2)	198 (13.3)	NA
Ileocolonic or unspecific CD	1,129 (24.0)	1,129 (76.0)	NA
Ulcerative proctitis	244 (5.2)	NA	244 (7.6)
Left sided UC	152 (3.2)	NA	152 (4.7)
Pancolitis	46 (1.0)	NA	46 (1.4)
Unspecific UC	2,781 (59.1)	NA	2,781 (86.3)
Disease behavior [*n* (%)]			
Non-stricturing, non-penetrating	552 (37.2)	552 (37.2)	NA
Stricturing	349 (23.5)	349 (23.5)	NA
Penetrating	42 (2.8)	42 (2.8)	NA
Unspecific	542 (36.5)	542 (36.5)	NA
Nonsteroidal anti-inflammatory drugs use [*n* (%)]	1,911 (40.6)	644 (43.4)	1,267 (39.3)
Aminosalicylate use [*n* (%)]	1,733 (36.8)	422 (28.4)	1,311 (40.7)
Corticosteroid use [*n* (%)]	313 (6.6)	118 (7.9)	195 (6.1)
Immunomodulators use [*n* (%)]	547 (11.6)	227 (15.3)	320 (9.9)
Systolic blood pressure [mean ± SD (mmHg)]	138.4 (19.4)	137.6 (19.5)	138.7 (19.3)
Diastolic blood pressure [mean ± SD (mmHg)]	81.3 (10.5)	81.1 (10.8)	81.4 (10.3)
C-reactive protein [mean ± SD (mg/L)]	3.6 (5.8)	4.2 (6.6)	3.3 (5.3)
Cholesterol [mean ± SD (mmol/L)]	5.5 (1.1)	5.3 (1.1)	5.6 (1.1)
Triglycerides [mean ± SD (mmol/L)]	1.8 (1.0)	1.9 (1.1)	1.7 (1.0)
Apolipoprotein (a) [mean ± SD (g/L)]	1.5 (0.3)	1.5 (0.3)	1.5 (0.3)

Note: Mean ± SD values and number (percentages) are reported for continuous and categorical variables, respectively. Missing values were imputed using single imputations. BMI, body mass index; CD, Crohn's disease; IBD, inflammatory bowel disease; NA, not applicable; SD, standard deviation; UC, ulcerative colitis.
[a]Ethnicity was categorized into "White" (White, British, Irish, and any other White background) and "Others" (Mixed, Asian or Asian British, Black or Black British, Chinese, and other ethnic groups) due to limited number was limited in the study sample.

significant (HR per IQR = 1.19; 95% CI: 0.95, 1.49, $p = 0.133$). When investigating associations between air pollutants and enterotomy by sources of admission to the hospital (Table S4), we observed that individuals exposed to the highest quartile of $PM_{2.5}$ had a higher risk of emergency surgery in comparison with individuals exposed to the lowest quartile of $PM_{2.5}$ among IBD (HR = 1.86; 95% CI: 1.01, 3.44, $p = 0.048$). In individuals with CD, an IQR increase in NO_x, NO_2, PM_{10}, and $PM_{2.5}$ was associated with 31% (95% CI: 6%, 62%, $p = 0.012$), 57% (95% CI: 12%, 120%, $p = 0.008$), 52% (95% CI: 3%, 123%, $p = 0.034$), and 46% (95% CI: 10%, 92%, $p = 0.008$) greater risk of emergency enterotomy, respectively. We did not observe any significant associations between air pollution and the risk of elective enterotomy in IBD, CD, and UC (all $p > 0.05$).

For gastrointestinal cancer, we did not observe any significant associations between air pollution and the risk of gastrointestinal cancer among individuals with IBD, CD, and UC (all $p > 0.05$; Table 4). In individuals with IBD, the HRs per IQR increment of NO_x (0.98), NO_2 (1.03), PM_{10} (1.00), and $PM_{2.5}$ (0.97) for gastrointestinal cancer were close to 1, with wide confidence intervals. Analyses by quartiles did not show evidence of an association between greater exposure and increased risk.

We observed an IQR increase in NO_x, NO_2, PM_{10}, and $PM_{2.5}$ was associated with 10% (95% CI: 1%, 20%, $p = 0.036$), 16% (95% CI: 3%, 29%, $p = 0.010$), 15% (95% CI: 3%, 30%, $p = 0.015$), and 14% (95% CI: 2%, 28%, $p = 0.019$) increased risk of all-cause mortality among individuals with IBD, respectively (Table 5). In individuals with CD, we only observed significant associations between PM_{10} and risk of all-cause mortality (HR per IQR = 1.26; 95% CI: 1.04, 1.53, $p = 0.017$), whereas an IQR increase in NO_x (HR = 1.14; 95% CI: 1.01, 1.29, $p = 0.030$) and $PM_{2.5}$ (HR = 1.17; 95% CI: 1.01, 1.36, $p = 0.030$) were associated higher risk of all-cause mortality in UC, respectively. For per IQR increase in air pollutants, we observed significant associations of NO_2 (HR = 1.22; 95% CI: 1.02, 1.47, $p = 0.034$) and PM_{10} (HR = 1.26; 95% CI: 1.04, 1.54, $p = 0.020$) with cardiovascular disease-specific mortality and significant associations of NO_x (HR = 1.15; 95% CI: 1.03, 1.29, $p = 0.014$) and $PM_{2.5}$ (HR = 1.17; 95% CI: 1.01, 1.37, $p = 0.047$) with cancer-specific mortality among individuals with IBD (Table S5).

When investigating the associations of air pollutants (per IQR increment) with risk of enterotomy and all-cause mortality among individuals with IBD by phenotypes (Table S6), we observed

Table 2. Descriptive statistics of pollutants and correlation matrix among participants with IBD in the UK Biobank Study, 2006–2010.

Air pollutants ($\mu g/m^3$)	Mean ± SD	Median (IQR)	Min and Max	Pearson correlation coefficients			
				NO_x	NO_2	PM_{10}	$PM_{2.5}$
NO_x	43.9 (15.2)	42.0 (34.8, 50.4)	19.7, 247.5	1	0.789	0.672	0.864
NO_2	29.0 (8.9)	27.9 (23.0, 33.4)	10.0, 86.6	0.789	1	0.792	0.736
PM_{10}	19.3 (1.9)	19.1 (18.0, 20.3)	13.7, 28.6	0.672	0.792	1	0.652
$PM_{2.5}$	10.0 (1.1)	9.9 (9.3, 10.6)	8.2, 20.7	0.864	0.736	0.652	1

Note: IBD, inflammatory bowel disease; IQR, interquartile range; max, maximum; min, minimum; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; PM, particulate matter; $PM_{2.5}$ PM with aerodynamic diameter ≤2.5 μm; PM_{10}, PM with aerodynamic diameter ≤10 μm; SD, standard deviation.

significant associations between each of the four air pollutants and enterotomy among nonstricturing and nonpenetrating CD (B1 behavior, all $p < 0.05$). For all-cause mortality, we only observed a significant association between PM_{10} and all-cause mortality among stricturing CD (B2 behavior, $p = 0.034$). Analysis for associations between air pollution and gastrointestinal cancer was not conducted because there were limited incident cases in most phenotypes.

Mediation Analysis

According to results in multivariable linear regression (Table S7), exposures to $PM_{2.5}$, PM_{10}, and NO_x were significantly associated with three (C-reactive protein, INFLA score, and lymphocyte count), two (C-reactive protein and eosinophil count), and one (C-reactive protein) serum biomarker, respectively. NO_2 was not significantly associated with any of the potential biomarkers. Mediation analysis (Figure 1) showed that 15.2% and 9.1% of the associations between $PM_{2.5}$ and enterotomy among individuals with IBD were mediated by serum C-reactive protein and INFLA-score, respectively, whereas 11.9% of the associations between $PM_{2.5}$ and all-cause mortality among individuals with IBD were mediated by serum C-reactive protein. We also observed 7.7% and 5.7% of the associations of PM_{10} and NO_x with all-cause mortality were mediated by C-reactive protein.

Subgroup Analysis and Sensitivity Analysis

We did not observe the effect modification of age, sex, physical activity, and smoking status in associations between air pollution and risk of enterotomy, gastrointestinal cancer, and all-cause mortality among individuals with IBD (all p-interaction >0.05; Table S8). We found that following a healthy diet could modify the associations of $PM_{2.5}$ with enterotomy (p-interaction $= 0.044$) and the associations of four air pollutants with gastrointestinal cancer and all-cause mortality (all p-interaction <0.05). Compared with those following a healthy diet, there was a stronger association between $PM_{2.5}$ and enterotomy [HR = 1.31; (95% CI: 1.07, 1.60) vs. HR = 1.00; (95% CI: 0.83, 1.21) per IQR] among individuals with an unhealthy diet. The interaction pattern was similar in the associations of four air pollutants with all-cause mortality by healthy/unhealthy diet. Although there was no significant main effect for the associations between air pollutants and gastrointestinal cancer in the primary analysis, their associations with gastrointestinal cancer [HRs and 95% CIs unhealthy vs. healthy diet: NO_x HR = 1.41; (95% CI: 1.08, 1.83) vs. HR = 0.81; (95% CI: 0.62, 1.04); NO_2 HR = 1.49; (95% CI: 1.06, 2.09) vs. HR = 0.90; (95% CI: 0.70, 1.16); PM_{10} HR = 1.41; (95% CI: 0.96, 2.07) vs. HR = 0.88; (95% CI: 0.68, 1.13); $PM_{2.5}$ HR = 1.37; (95% CI: 0.98, 1.91) vs. HR = 0.83; (95% CI: 0.63, 1.08); per IQR] were stronger among individuals with unhealthy diet.

In sensitivity analysis (Table S9), all four air pollutants showed a nonsignificant positive trend in association with gastrointestinal cancers when restricted to individuals who had at least 10 y of residence at baseline. The results were consistent with primary findings or maintained similar magnitude when additionally adjusted for Charlson Comorbidity Index (Table S10), additionally adjusted for baseline disease duration (Table S11), additionally adjusted for indoor air pollution-related variables (Table S12), adjusted for TDI instead of household income (Table S13), excluding gastrointestinal cancer or death events in the first 3 y of follow-up (Table S14), and excluding individuals with a baseline history of enterotomy (Table S15). Results from the competing risk model demonstrated inverse but nonsignificant associations between air pollution and gastrointestinal cancer with wide 95% CIs (all $p > 0.10$; Table S16).

Discussion

In this prospective cohort study, we followed 4,708 individuals with IBD to evaluate the associations between four air pollutants and the risk of adverse outcomes including enterotomy, gastrointestinal cancer, and all-cause mortality. We found that per IQR increment in $PM_{2.5}$ exposure was significantly associated with a 16% increased risk of enterotomy, whereas each IQR increment in NO_x, NO_2, PM_{10}, and $PM_{2.5}$ was associated with 10%, 16%, 15%, and 14% increased risk of all-cause mortality among individuals with IBD, respectively. We did not observe significant associations between air pollutants and the risk of gastrointestinal cancer in individuals with IBD in the primary analysis. Mediation analysis demonstrated that 5.7%–15.2% of associations of air pollutants with risk of enterotomy and all-cause mortality can be mediated by the C-reactive protein levels and/or INFLA-scoring. Subgroup analysis demonstrated the effect modification of diet in the associations between air pollution and adverse outcomes of IBD. Specifically, positive associations between air pollutants and gastrointestinal cancer were observed among individuals with an unhealthy diet.

$PM_{2.5}$ passes through the lungs into circulation along with toxic gases such as NO_2, and they together initiate, accelerate, and exacerbate adverse health outcomes in the human body.[10] When air pollutants enter gut tissue, they may cause tight junction protein rearrangements of epithelial cells, resulting in increased intestinal barrier permeability.[40,41] In addition, PM exposure might induce systemic inflammation, which was considered a major cause of the negative health impacts of PM.[10] Previous studies have also shown that air pollution leads to alterations in the intestinal microbiota, which enhances vulnerability to mucosal inflammation.[42] The aforementioned pathways may promote or even exacerbate adverse outcomes of IBD in the context that individuals with IBD are characterized by persistent inflammation and changed gut microbiota.

To our knowledge, the association between $PM_{2.5}$ and the risk of enterotomy among IBD patients has never been assessed by any previous epidemiological study. However, indirect evidence on other clinical outcomes of IBD may imply that the existence of such an association is plausible. Two ecological studies in the United States and China both demonstrated a positive correlation between $PM_{2.5}$ exposure and hospitalization of IBD.[5,6] The significant associations between $PM_{2.5}$ and emergency surgery (Table S4) and significant associations among nonstricturing

Table 3. Associations of air pollutants with risk of enterotomy in individuals with IBD, CD, and UC in the UK Biobank Study, mean follow-up of 12 y.

Air pollutants in quartiles ($\mu g/m^3$)	IBD ($n = 4{,}708$)					CD ($n = 1{,}485$)			UC ($n = 3{,}233$)		
	Cases/person-years	HR (95% CI)[a]	*p-Value*	HR (95% CI)[b]	*p*-Value[c]	Cases/person-years	HR (95% CI)[b]	*p*-Value	Cases/person-years	HR (95% CI)[b]	*p*-Value
NO_x											
Per IQR (15.6)	—	1.11 (1.00, 1.23)	0.059	1.10 (0.98, 1.23)	0.091	—	1.14 (0.98, 1.32)	0.082	—	1.16 (0.96, 1.40)	0.115
Q1 (19.7 to <34.8)	70/13,719	Ref	—	Ref	—	29/4,318	Ref		41/9,503	Ref	—
Q2 (34.8 to <42.0)	56/13,758	0.80 (0.56, 1.13)	0.202	0.72 (0.51, 1.03)	0.071	23/4,159	0.76 (0.44, 1.32)	0.324	33/9,651	0.75 (0.42, 1.35)	0.338
Q3 (42.0 to <50.4)	70/13,541	0.99 (0.71, 1.38)	0.949	0.93 (0.66, 1.29)	0.650	31/4,366	1.03 (0.62, 1.72)	0.911	39/9,212	1.19 (0.69, 2.04)	0.527
Q4 (50.4–247.5)	69/13,823	0.98 (0.70, 1.37)	0.908	0.93 (0.66, 1.30)	0.660	32/4,108	1.04 (0.62, 1.72)	0.892	37/9,751	1.12 (0.65, 1.94)	0.684
p-Trend	—	—	0.791	—	0.975	—	—	0.626	—	—	0.353
NO_2											
Per IQR (10.4)	—	1.07 (0.94, 1.23)	0.310	1.06 (0.92, 1.22)	0.431	—	1.12 (0.91, 1.37)	0.294	—	1.12 (0.90, 1.40)	0.301
Q1 (10.0 to <23.0)	65/13,706	Ref	—	Ref	—	27/4,413	Ref	—	38/9,379	Ref	—
Q2 (23.0 to <27.9)	53/13,767	0.82 (0.57, 1.17)	0.273	0.77 (0.54, 1.11)	0.167	21/4,147	0.78 (0.44, 1.39)	0.404	32/9,683	1.00 (0.55, 1.83)	0.990
Q3 (27.9 to <33.4)	79/13,691	1.21 (0.87, 1.69)	0.246	1.15 (0.83, 1.60)	0.410	35/4,250	1.25 (0.75, 2.08)	0.384	44/9,476	1.68 (0.98, 2.89)	0.060
Q4 (33.4–86.6)	68/13,677	1.04 (0.74, 1.46)	0.825	0.99 (0.70, 1.39)	0.947	32/4,142	1.15 (0.68, 1.92)	0.609	36/9,579	1.11 (0.62, 1.99)	0.732
p-Trend	—	—	0.358	—	0.515	—	—	0.307	—	—	0.357
PM_{10}											
Per IQR (2.3)	—	1.08 (0.93, 1.24)	0.316	1.07 (0.92, 1.23)	0.388	—	1.15 (0.93, 1.43)	0.185	—	0.99 (0.79, 1.26)	0.960
Q1 (13.7 to <18.0)	56/13,843	Ref	—	Ref		20/4,215	Ref	—	36/9,688	Ref	—
Q2 (18.0 to <19.1)	70/13,824	1.25 (0.88, 1.77)	0.222	1.21 (0.85, 1.72)	0.291	31/4,477	1.56 (0.89, 2.75)	0.122	39/9,415	1.06 (0.61, 1.84)	0.843
Q3 (19.1 to <20.3)	70/13,650	1.27 (0.89, 1.80)	0.185	1.23 (0.87, 1.75)	0.244	33/4,192	1.57 (0.90, 2.75)	0.114	37/9,490	1.27 (0.74, 2.18)	0.391
Q4 (20.3–28.6)	69/13,524	1.23 (0.86, 1.75)	0.251	1.20 (0.84, 1.71)	0.310	31/4,068	1.48 (0.84, 2.61)	0.176	38/9,524	0.97 (0.55, 1.71)	0.908
p-Trend	—	—	0.275	—	0.333	—	—	0.225	—	—	0.919
$PM_{2.5}$											
Per IQR (1.3)	—	1.16 (1.01, 1.33)	0.030	1.16 (1.00, 1.34)	0.043	—	1.24 (1.04, 1.47)	0.017	—	1.19 (0.95, 1.49)	0.133
Q1 (8.2 to <9.3)	53/13,900	Ref	—	Ref	—	21/4,470	Ref	—	32/9,506	Ref	—
Q2 (9.3 to <9.9)	70/13,601	1.35 (0.94, 1.92)	0.102	1.36 (0.95, 1.95)	0.090	28/4,237	1.37 (0.78, 2.42)	0.275	42/9,423	1.63 (0.90, 2.94)	0.105
Q3 (9.9 to <10.6)	63/13,603	1.21 (0.84, 1.75)	0.297	1.19 (0.82, 1.72)	0.366	23/4,137	1.14 (0.63, 2.07)	0.670	40/9,525	1.56 (0.86, 2.81)	0.142
Q4 (10.6–20.7)	79/13,737	1.51 (1.07, 2.14)	0.020	1.58 (1.09, 2.28)	0.015	43/4,107	2.09 (1.24, 3.54)	0.006	36/9,663	1.51 (0.83, 2.76)	0.176
p-Trend	—	—	0.044	—	0.040	—	—	0.010	—	—	0.249

Note: —, no data; BMI, body mass index; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; IQR, interquartile range; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; PM, particulate matter; $PM_{2.5}$ PM with aerodynamic diameter ≤ 2.5 μm; PM_{10}, PM with aerodynamic diameter ≤ 10 μm; Ref, reference; UC, ulcerative colitis.

[a]Based on Cox proportional model adjusted for age, sex, ethnicity.

[b]Based on Cox proportional model adjusted for age, sex, ethnicity, assessment centers, household income, smoking status, education, BMI, physical activity, healthy diet, alcohol consumption, baseline related surgery history, medication (use of nonsteroidal anti-inflammatory drugs, amino salicylates, corticosteroids, and immunomodulators).

[c]*p*-Value <0.05 was considered statistically significant.

Table 4. Associations of air pollutants with risk of gastrointestinal cancer in individuals with IBD, CD, and UC in the UK Biobanks Study, mean follow-up of 12 y.

Air pollutants in quartiles (μg/m^3)	IBD ($n = 4,708$)					CD ($n = 1,485$)			UC ($n = 3,233$)		
	Cases/person-years	HR (95% CI)[a]	*p*-Value	HR (95% CI)[b]	*p*-Value[c]	Cases/person-years	HR (95% CI)[b]	*p*-Value	Cases/person-years	HR (95% CI)[b]	*p*-Value
NO_x											
Per IQR (15.6)	—	0.98 (0.82, 1.18)	0.843	0.98 (0.81, 1.18)	0.807	—	0.86 (0.56, 1.31)	0.479	—	1.03 (0.83, 1.28)	0.782
Q1 (19.7 to <34.8)	34/14,031	Ref	—	Ref	—	6/4,486	Ref	—	28/9,493	Ref	—
Q2 (34.8 to <42.0)	24/13,964	0.73 (0.43, 1.22)	0.229	0.71 (0.42, 1.20)	0.201	7/4,241	1.36 (0.45, 4.11)	0.591	17/9,697	0.59 (0.32, 1.09)	0.090
Q3 (42.0 to <50.4)	39/13,865	1.16 (0.73, 1.85)	0.521	1.16 (0.73, 1.85)	0.523	14/4,507	2.64 (1.00, 7.00)	0.053	25/9,207	0.90 (0.52, 1.55)	0.695
Q4 (50.4–247.5)	27/14,121	0.89 (0.54, 1.46)	0.640	0.87 (0.52, 1.44)	0.587	2/4,282	0.43 (0.08, 2.14)	0.299	25/9,722	0.96 (0.56, 1.64)	0.873
p-Trend	—	—	0.893	—	0.926	—	—	0.999	—	—	0.825
NO_2											
Per IQR (10.4)	—	1.04 (0.85, 1.28)	0.695	1.03 (0.84, 1.27)	0.745	—	0.91 (0.58, 1.44)	0.689	—	1.09 (0.86, 1.37)	0.487
Q1 (10.0 to <23.0)	34/13,958	Ref	—	Ref	—	6/4,564	Ref	—	28/9,357	Ref	—
Q2 (23.0 to <27.9)	28/14,003	0.84 (0.51, 1.39)	0.495	0.84 (0.51, 1.38)	0.485	9/4,215	1.75 (0.61, 4.98)	0.295	19/9,665	0.68 (0.38, 1.21)	0.190
Q3 (27.9 to <33.4)	30/14,094	0.90 (0.55, 1.47)	0.681	0.92 (0.56, 1.51)	0.738	10/4,428	1.87 (0.67, 5.24)	0.233	20/9,560	0.72 (0.41, 1.29)	0.272
Q4 (33.4–86.6)	32/13,926	1.02 (0.63, 1.65)	0.947	1.01 (0.62, 1.64)	0.971	4/4,308	0.86 (0.24, 3.11)	0.819	28/9,538	1.04 (0.61, 1.77)	0.874
p-Trend	—	—	0.900	—	0.897	—	—	0.992	—	—	0.845
PM_{10}											
Per IQR (2.3)	—	1.00 (0.81, 1.24)	0.990	1.00 (0.81, 1.24)	0.995	—	0.79 (0.49, 1.25)	0.312	—	1.09 (0.86, 1.39)	0.488
Q1 (13.7 to <18.0)	33/14,017	Ref	—	Ref	—	11/4,270	Ref	—	22/9,672	Ref	—
Q2 (18.0 to <19.1)	30/14,185	0.91 (0.55, 1.48)	0.694	0.91 (0.55, 1.50)	0.711	7/4,648	0.58 (0.22, 1.50)	0.261	23/9,451	1.08 (0.60, 1.93)	0.807
Q3 (19.1 to <20.3)	31/13,985	0.98 (0.60, 1.60)	0.929	0.98 (0.60, 1.60)	0.941	8/4,358	0.78 (0.31, 1.97)	0.602	23/9,512	1.09 (0.60, 1.95)	0.780
Q4 (20.3–28.6)	30/13,794	0.97 (0.59, 1.59)	0.899	0.96 (0.58, 1.58)	0.868	3/4,239	0.31 (0.09, 1.14)	0.097	27/9,485	1.29 (0.73, 2.28)	0.375
p-Trend	—	—	0.974	—	0.943	—	—	0.120	—	—	0.390
$PM_{2.5}$											
Per IQR (1.3)	—	0.98 (0.79, 1.21)	0.824	0.97 (0.78, 1.20)	0.789	—	0.89 (0.57, 1.40)	0.624	—	1.01 (0.79, 1.30)	0.920
Q1 (8.2 to <9.3)	35/14,077	Ref		Ref		9/4,573	Ref		26/9,427	Ref	
Q2 (9.3 to <9.9)	27/13,898	0.78 (0.47, 1.29)	0.331	0.76 (0.46, 1.26)	0.295	6/4,372	0.82 (0.29, 2.36)	0.713	21/9,489	0.77 (0.43, 1.37)	0.372
Q3 (9.9 to <10.6)	35/13,898	1.03 (0.65, 1.65)	0.886	1.03 (0.65, 1.66)	0.887	9/4,245	1.30 (0.50, 3.35)	0.593	26/9,549	0.99 (0.57, 1.71)	0.977
Q4 (10.6–20.7)	27/14,108	0.82 (0.50, 1.36)	0.438	0.80 (0.48, 1.33)	0.394	5/4,325	0.69 (0.23, 2.12)	0.521	22/9,654	0.85 (0.48, 1.50)	0.573
p-Trend	—	—	0.698	0.97 (0.82, 1.13)	0.662	—	—	0.786	—	—	0.788

Note: —, no data; BMI, body mass index; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; IQR, interquartile range; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; PM, particulate matter; $PM_{2.5}$ PM with aerodynamic diameter ≤2.5 μm; PM_{10}, PM with aerodynamic diameter ≤10 μm; Ref, reference; UC, ulcerative colitis.

[a]Based on Cox proportional model adjusted for age, sex, ethnicity.

[b]Based on Cox proportional model adjusted for age, sex, ethnicity, assessment centers, household income, smoking status, education, BMI, physical activity, healthy diet, alcohol consumption, baseline related surgery history, medication (use of nonsteroidal anti-inflammatory drugs, amino salicylates, corticosteroids, and immunomodulators).

[c]*p*-Value <0.05 was considered statistically significant.

Table 5. Associations of air pollutants with risk of all-cause mortality in individuals with IBD, CD, and UC in the UK Biobank study, mean follow-up of 12 y.

Air pollutants in quartiles ($\mu g/m^3$)	IBD ($n = 4{,}708$)					CD ($n = 1{,}485$)			UC ($n = 3{,}233$)		
	Cases/person-years	HR (95% CI)[a]	*p*-Value	HR (95% CI)[b]	*p*-Value[c]	Cases/person-years	HR (95% CI)[b]	*p*-Value	Cases/person-years	HR (95% CI)[b]	*p*-Value
NO_x											
Per IQR (15.6)	—	1.12 (1.03, 1.21)	0.008	1.10 (1.01, 1.20)	0.036	—	1.04 (0.89, 1.21)	0.637	—	1.14 (1.01, 1.29)	0.030
Q1 (19.7 to <34.8)	82/13,835	Ref	—	Ref	—	28/4,425	Ref	—	54/9,360	Ref	—
Q2 (34.8 to <42.0)	118/13,701	1.51 (1.14, 2.01)	0.004	1.44 (1.08, 1.91)	0.012	41/4,165	1.57 (0.96, 2.54)	0.070	77/9,510	1.37 (0.97, 1.95)	0.076
Q3 (42.0 to <50.4)	114/13,580	1.49 (1.12, 1.98)	0.006	1.39 (1.04, 1.85)	0.026	39/4,422	1.33 (0.82, 2.18)	0.250	75/9,013	1.41 (0.99, 2.01)	0.058
Q4 (50.4–247.5)	106/13,788	1.53 (1.15, 2.04)	0.004	1.39 (1.04, 1.86)	0.025	36/4,178	1.30 (0.79, 2.14)	0.301	70/9,489	1.37 (0.95, 1.96)	0.088
p-Trend	—	—	0.007	—	0.049	—	—	0.481	—	—	0.106
NO_2											
Per IQR (10.4)	—	1.18 (1.06, 1.31)	0.003	1.16 (1.03, 1.29)	0.010	—	1.17 (0.98, 1.41)	0.079	—	1.13 (0.98, 1.30)	0.091
Q1 (10.0 to <23.0)	92/13,825	Ref	—	Ref	—	32/4,521	Ref	—	60/9,269	Ref	—
Q2 (23.0 to <27.9)	110/13,765	1.26 (0.95, 1.66)	0.107	1.21 (0.92, 1.60)	0.178	38/4,149	1.29 (0.80, 2.07)	0.290	72/9,494	1.19 (0.84, 1.68)	0.319
Q3 (27.9 to <33.4)	98/13,822	1.13 (0.85, 1.50)	0.405	1.05 (0.79, 1.39)	0.755	29/4,360	0.91 (0.55, 1.51)	0.709	69/9,356	1.10 (0.77, 1.56)	0.592
Q4 (33.4–86.6)	120/13,491	1.58 (1.20, 2.07)	0.001	1.48 (1.13, 1.95)	0.005	45/4,161	1.55 (0.98, 2.46)	0.059	75/9,254	1.42 (1.01, 2.00)	0.045
p-Trend	—	—	0.004	—	0.018	—	—	0.162	—	—	0.079
PM_{10}											
Per IQR (2.3)	—	1.04 (1.01, 1.06)	0.003	1.15 (1.03, 1.30)	0.015	—	1.26 (1.04, 1.53)	0.017	—	1.08 (0.93, 1.26)	0.299
Q1 (13.7 to <18.0)	93/13,810	Ref	—	Ref	—	26/4,245	Ref	—	67/9,493	Ref	—
Q2 (18.0 to <19.1)	95/13,906	1.03 (0.77, 1.37)	0.854	1.01 (0.76, 1.34)	0.946	35/4,546	1.34 (0.80, 2.23)	0.263	60/9,278	0.87 (0.62, 1.24)	0.451
Q3 (19.1 to <20.3)	121/13,715	1.39 (1.06, 1.82)	0.017	1.35 (1.03, 1.76)	0.032	39/4,270	1.60 (0.97, 2.65)	0.067	82/9,331	1.18 (0.85, 1.64)	0.317
Q4 (20.3–28.6)	111/13,472	1.38 (1.05, 1.82)	0.022	1.34 (1.02, 1.77)	0.037	44/4,130	1.84 (1.13, 3.01)	0.015	67/9,272	1.12 (0.80, 1.57)	0.511
P-Trend	—	—	0.004	—	0.008	—	—	0.011	—	—	0.237
$PM_{2.5}$											
Per IQR (1.3)	—	1.02 (1.01, 1.03)	0.003	1.14 (1.02, 1.28)	0.019	—	1.10 (0.91, 1.33)	0.325	—	1.17 (1.01, 1.36)	0.030
Q1 (8.2 to <9.3)	86/13,865	Ref		Ref		33/4,508	Ref		53/9,284	Ref	
Q2 (9.3 to <9.9)	120/13,605	1.43 (1.09, 1.89)	0.011	1.38 (1.04, 1.82)	0.023	41/4,280	1.33 (0.84, 2.12)	0.223	79/9,289	1.40 (0.99, 1.98)	0.059
Q3 (9.9 to <10.6)	102/13,650	1.25 (0.94, 1.67)	0.125	1.16 (0.87, 1.55)	0.307	32/4,161	1.05 (0.64, 1.71)	0.858	70/9,389	1.22 (0.85, 1.76)	0.272
Q4 (10.6–20.7)	112/13,783	1.46 (1.10, 1.94)	0.008	1.36 (1.02, 1.80)	0.035	38/4,242	1.24 (0.77, 1.98)	0.377	74/9,411	1.40 (0.98, 2.00)	0.062
p-Trend	—	—	0.031	—	0.118	—	—	0.613	—	—	0.140

Note: —, no data; BMI, body mass index; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; IQR, interquartile range; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; PM, particulate matter; $PM_{2.5}$ PM with aerodynamic diameter ≤ 2.5 μm; PM_{10}, PM with aerodynamic diameter ≤ 10 μm; Ref, reference; UC, ulcerative colitis.

[a]Based on Cox proportional model adjusted for age, sex, ethnicity.

[b]Based on Cox proportional model adjusted for age, sex, ethnicity, assessment centers, household income, smoking status, education, BMI, physical activity, healthy diet, alcohol consumption, baseline related surgery history, medication (use of nonsteroidal anti-inflammatory drugs, amino salicylates, corticosteroids, and immunomodulators).

[c]*p*-Value <0.05 was considered statistically significant.

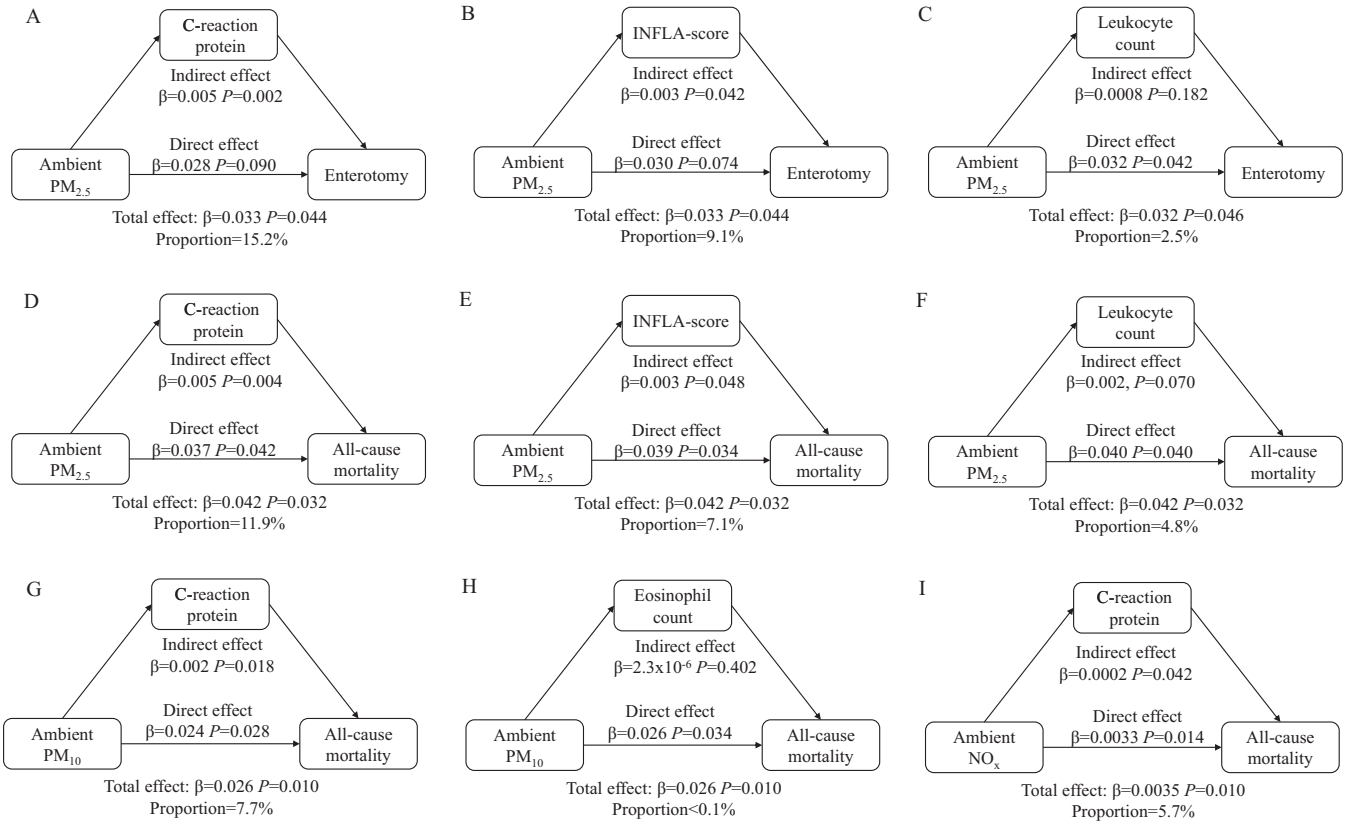

Figure 1. Mediation analysis in associations of air pollutants with enterotomy and all-cause mortality among participants with inflammatory bowel disease ($n = 4{,}708$) in the UK Biobank Study. (A–C): Direct and indirect associations of $PM_{2.5}$ with enterotomy via C-reactive protein (A), INFLA-score (B), and leukocyte count (C); (D–F) direct and indirect associations of $PM_{2.5}$ with all-cause mortality via C-reactive protein (D), INFLA-score (E), and leukocyte count (F); (G–H) direct and indirect associations of PM_{10} with all-cause mortality via C-reactive protein (G) and eosinophil count (H); (E): direct and indirect associations of NO_x with all-cause mortality via C-reactive protein. $p < 0.05$ was considered statistically significant. Based on the fully adjusted model (Cox model). INFLA-score is a compound indicator containing C-reactive protein, white blood cell, platelet count, and the neutrophil to lymphocyte ratio; Note: NO_x, nitrogen oxides; PM, particulate matter; $PM_{2.5}$ PM with aerodynamic diameter ≤2.5 μm; PM_{10}, PM with aerodynamic diameter ≤10 μm.

and nonpenetrating CD (Table S6) both support the hypothesis that it is the intestinal damage caused by air pollution rather than the preexisting obstructive symptoms that cause enterotomy. Findings from experimental studies also supported the observed association from a perspective of biological relevance. An experimental study based on animal models showed that inhalational exposure to $PM_{2.5}$ can increase small intestinal permeability and accompany an inflammatory response.[43] In our mediation analysis, only 10%–15% of the associations can be explained by inflammation. This implied that bowel weakness/susceptibility could be worsened by air pollution via other pathways. This may have been achieved by significant dysbiosis of gut microbiota and systemic and local metabolic alterations.[44]

We did not observe any significant associations between the four air pollutants and incident gastrointestinal cancer among individuals with IBD. The ESCAPE study, which covered 11 European cohorts using the same air pollution estimation as ours, did not find any significant association of NO_x and NO_2 with gastric cancer, which is consistent with our findings.[45] A Danish study including more than 50,000 people also did not find any significant association between NO_x (per 100 $\mu g/m^3$) and gastric, colon, and rectal cancers (all HRs <1) either.[46] For PM_{10} and $PM_{2.5}$, positive associations between long-term exposure to PMs and the risk of overall gastrointestinal cancer have been reported by a recent meta-analysis.[8] Given that previous studies reporting significant positive associations often had large sample sizes of 100,000 or more,[45] the null finding of our study might be explained by the inadequate study power to detect any small to moderate associations. In addition, the wide CIs of the effect estimates reported in our study drive the direction of the association to be null. Another explanation for the null association is probably because of the low level of air pollution in the UK Biobank cohort, which may provide insufficient variation of air pollution exposure to cause a significant difference in the risk of gastrointestinal cancer development. This may be partly reflected in our restriction of the analysis to individuals who had at least 10 y of residence at baseline, with all four air pollutants showing a nonsignificant positive trend in association with gastrointestinal cancer.

In our study, participants with IBD were more vulnerable to increased risk of mortality than the general population when exposed to air pollution. The air pollution level was relatively low in our study. For instance, the annual mean ambient $PM_{2.5}$ concentration ranges from 8.2 to 20.1 $\mu g/m^3$, with 100% and 96% of the cohort exposed to levels lower than the annual European Union Ambient Air Quality Directives (25 $\mu g/m^3$) and the National Ambient Air Quality Standard set by the U.S. Environmental Protection Agency (12 $\mu g/m^3$). Previous large cohort studies in Europe and Canada found positive associations of exposure to low-level $PM_{2.5}$, PM_{10}, NO_x, and NO_2 with increased risk of mortality in more than 10 million adults.[39,47,48] In the population-based Canadian Census Health and Environment Cohort, long-term exposures to $PM_{2.5}$ (per 5 $\mu g/m^3$, ranging from 0.9 to 17.6 $\mu g/m^3$) and NO_2 (per 15.2 $\mu g/m^3$, ranging from 0 to 96.8 $\mu g/m^3$) were associated with 0.35% and 0.52% increased risk of mortality, respectively.[47] In line with previous studies, our findings support the associations of higher

air pollutant exposures with increased mortality among individuals with IBD. However, the HR per IQR increase in air pollutants like $PM_{2.5}$ (1.3 $\mu g/m^3$) that we report for all-cause mortality was greater (HR = 1.14 vs. 1.035) than HRs previously estimated in the general population in Canada,[47] suggesting that individuals with IBD may get more health benefits than the general population from reducing air pollution incrementally even in areas with relatively clean air.

Results from mediation analysis support the hypothesis that systemic inflammation triggered by $PM_{2.5}$ and other air pollutants promotes the adverse outcomes of IBD. However, current inflammation biomarkers in our analysis mediated only 5.7%–15.7% of associations between air pollutants and adverse outcomes, implying other potential mediating pathways. Previous literature has indicated that air pollutants such as $PM_{2.5}$ can also cause elevations in proinflammatory mediators associated with IBD including tumor necrosis factor-α, interleukin-1β, and interleukin-6,[10] but these cytokines were not available in our study. Second, because of the remitting-relapse course of IBD, a single measurement of inflammatory biomarkers at baseline may not reflect the actual long-term inflammatory status. Third, air pollutants may affect the intestinal and systemic health of patients with IBD through other noninflammatory pathways such as the microbiome.[44] Therefore, it is necessary to explore the mediation effect of multiple IBD-related intermediate biomarkers with close longitudinal monitoring data in the associations between air pollutants and adverse outcomes of IBD.

In subgroup analysis, we found that a healthy diet pattern modified the associations of air pollution with adverse clinical outcomes in individuals with IBD. Modification of diet was observed in the associations of NO_x, NO_2, and $PM_{2.5}$ and mortality in the general population in the UK Biobank using similar criteria evaluating healthy diet patterns.[39] Cardio-metabolically healthy dietary pattern characterized by a high intake of vegetables, fruits, fish, and whole grains and a low intake of processed and unprocessed red meat and refined grains, showed overall anti-inflammatory and antioxidative properties[30] and thus may mitigate the detrimental effect of air pollutants. IBD will promote chronic inflammation and was more vulnerable to unhealthy intake.[25] Because chronic inflammation was considered the main cause of colorectal cancer in IBD,[49] the positive associations between air pollutants and gastrointestinal cancer among individuals with an unhealthy diet had biological rationality. Therefore, our findings may be a starting point for future studies to confirm whether diet can be an effective intervention to prevent the harmful impact of air pollutants for IBD living in areas with air pollution concerns.

To our knowledge, this is the first prospective study providing information about the impact of ambient air pollution on the adverse outcomes among individuals with IBD. Strengths of our study include the large sample size, prospective design, and long-term follow-up in the UK Biobank that enabled the evaluation of important adverse outcomes in IBD. With reliable prediction models to measure air pollutants, the UK Biobank study also enabled us to assess the impact of major air pollutants.[16,17] Findings from our study highlighted the importance of air pollution abatement in improving the prognosis of IBD and reducing the IBD-related disease burden.

However, several limitations should be noted when interpreting the study findings. First, the baseline air pollution concentrations may not reflect the long-term air pollution during a long follow-up, and the latency of the associations of air pollutants with gastrointestinal cancer and mortality may confound the results in the primary analysis. However, previous studies indicated the stability of air pollution exposure.[18–21] Sensitivity analyses by restricting individuals living in their current address for more than 10 y excluding incident cases in the first 3-y follow-up suggested a consistently positive direction of the associations. Second, for any observational study, the possibility of residual confounding bias cannot be ruled out despite adjusting for multiple health-related factors. Third, the air pollution level is relatively low in our study, which needs further confirmation by studies conducted in areas with high air pollution levels. Fourth, although the ethical and socioeconomic backgrounds of individuals in the UK Biobank were varied, participants of this study were predominantly non-Hispanic White, which may limit the generalizability of the findings. Finally, UK Biobank did not have data on short-term outdoor air pollution exposure, other air pollutants, and indoor air exposure, which prevented us from further comprehensive exploration of the association between air pollution and adverse outcomes in IBD.

Conclusion

In this prospective cohort study, we found that exposure to ambient $PM_{2.5}$ was associated with an increased risk of enterotomy, whereas exposure to NO_x, NO_2, PM_{10}, and $PM_{2.5}$ were associated with all-cause mortality among individuals with IBD. These findings suggest that individuals with IBD will benefit over the lifelong disease course from local policies on reducing air pollution and may add extra meaning to the current health strategy for air pollution.

Acknowledgments

The authors are much obliged to the administer team of the UK Biobank as well as all the participants.

X.L. is supported by the Natural Science Fund for Distinguished Young Scholars of Zhejiang Province (LR22H260001). X.Y.W. is supported by National Natural Science Foundation of China (81970494) and Key Project of Research and Development Plan of Hunan Province (2019SK2041).

The ethical approval was granted for the UK Biobank by the North West–Haydock Research Ethics Committee (REC reference: 21/NW/0157). All participants provided informed consent through electronic signature at baseline assessment. This study was conducted with the UK Biobank Resource under application number 73595.

The data sets analyzed during the current study are available in a public, open-access repository (https://www.ukbiobank.ac.uk/).

All authors read and approved the final manuscript and participated as follows: J.C., conceptualization: leading; methodology: leading; formal analysis: equal; data curation: leading; and writing—review and editing: equal. L.D., conceptualization: supporting; methodology: equal; formal analysis: leading; writing—original draft: equal; and writing—review and editing: supporting. Y.S., conceptualization: supporting; methodology: supporting; writing—review and editing: supporting. S.Y., conceptualization: supporting; writing—review and editing: supporting. W.L., conceptualization: supporting; writing—review and editing: supporting. X.C., conceptualization: supporting; writing— review and editing: supporting. F.J., writing—review and editing: supporting. T.F., conceptualization: supporting; writing—original draft: equal; writing—review and editing: supporting. H.Z., conceptualization: supporting; writing—review and editing: supporting. M.D., conceptualization: leading; methodology: equal; formal analysis: supporting; writing—original draft: supporting; and writing—review and editing: equal. X.W., conceptualization: leading; data curation: equal; and funding acquisition: leading; writing—review and editing: equal. X.L.,

conceptualization: equal; data curation: equal; and funding acquisition: equal; and writing—review and editing: leading.

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